Process for the Preparation of Geminal Difluoroalkanes

The present invention relates to a process for the preparation of geminal difluoroalkanes, as well as to new compounds prepared by said process and their use as an intermediate of pharmaceutical products.

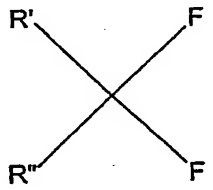
Owing to their advantageous biochemical properties geminal difluoroalkanes are of special significance, which is due to the fact that the CF_2-group is isopolar and isometric in relation to the ether oxygen and a R-CHOH group. According to conventional manufacturing processes, a corresponding ketone is converted to a geminal difluoroalkane using fluorophosgene (J. Am. Chem. Soc. 84 (1962) 4275), sulfur tetrafluoride (Org. Reactions 21 (1974) 1), DAST (Et_2NSF_3, J. Org. Chem. 40 (1975) 574) or trifluoroacetic acid anhydride or pyridine·HF (JP-A-63-054 332). Moreover, derivatized ketones such as hydrazones (J. Am. Chem. Soc. 109 (1987) 896), diazo compounds (J. Chem. Soc., Perkin Trans. 1 (1978) 1224) and thioketals (J. Org. Chem. 51 (1986) 3508) can be converted to geminal difluoroalkanes, respectively, using fluorine or halogen fluorides. In the present processes mainly gaseous and highly aggressive reagents are used that were generated using F_2 which involves a costly realisation of the conversion.

Recent literature has suggested to convert an unsubstituted oxime using a mixture of anhydrous hydrogen fluoride in ether in the presence of N_2O_4 (J. Fluorine Chem. 70 (1995) 207). However, the yield of this process is small. Concurrently, the conversion of an oxime using hydrogen fluoride in pyridine and nitrosyl tetrafluoroborate ($NOBF_4$) was published (Synlett (1994) 425). However, the reagent $NOBF_4$ is costly and ill- suited for the use in the industry. Furthermore, according to the above manufacturing processes, only unsubstituted oximes can be converted to the corresponding geminal difluoroalkanes.

Thus, it is the object of the present invention to overcome the above disadvantages of the prior art and to provide a process for the preparation of geminal difluoroalkanes which is specific, has sufficient yields, utilizes cost-effective reagents and which can also preferably be used for substituted difluoroalkanes.

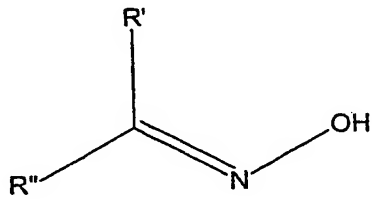
This object can be achieved by reacting an oxime with a nitrite and a complex consisting of hydrogen fluoride and an organic base.

Thus, the invention relates to a process for the preparation of a geminal difluoroalkane having the general formula (I),



(I)

wherein, independently from each other, R' and R" represent substituted alkyl-, aryl- or aralkyl or may be combined to form a cyclic system, characterized in that an oxime of the general formula (II)



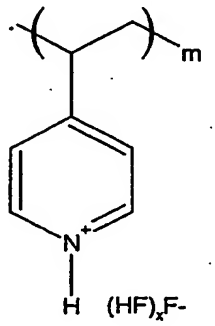
(II)

whereas R' and R" are defined as aforesaid, is converted using a nitrite and a complex comprising hydrogen fluoride and an organic base.

The oxime of the formula (II) is not particularly limited: in principle, any alkyl-, aryl- or aralkyl oxime can be used. If the oxime contains functional groups, these groups should be sufficiently stable with regard to acids and oxidants or be protected from fluorination accordingly. The oximes can be manufactured from the respective ketones by use of conventional processes. Thereby, 4-cyclohexanoneoxime carboxylic acid (esters) are parent compounds for particularly preferred difluoroalkanes according to the invention and novel, making them suitable for the use as intermediate compounds.

As the fluorination agent a combination of an hydrogen fluoride and an organic base may be used. Bases may be electron pair donors (Lewis bases) such as amines or ethers. In combination with an excess of hydrogen fluoride these organic bases containing free electron pairs form remarkably stable complexes of the general formula $BH^+(HF)_xF^-$, generally known as onium poly(hydrogen fluoride). Examples thereof are:

$R_2OH^+(HF)_xF^-$ (oxonium poly(hydrogen fluoride)), $C_5H_5NH^+(HF)_xF$ (pyridinium poly(hydrogen fluoride)), $R_3PH^+(HF)_xF^-$ (phosphonium poly(hydrogen fluoride)), $R_3NH^+(HF)_xF^-$ (ammonium poly(hydrogen fluoride)) and



(polyvinylpyridinium polyhydrogen fluoride).

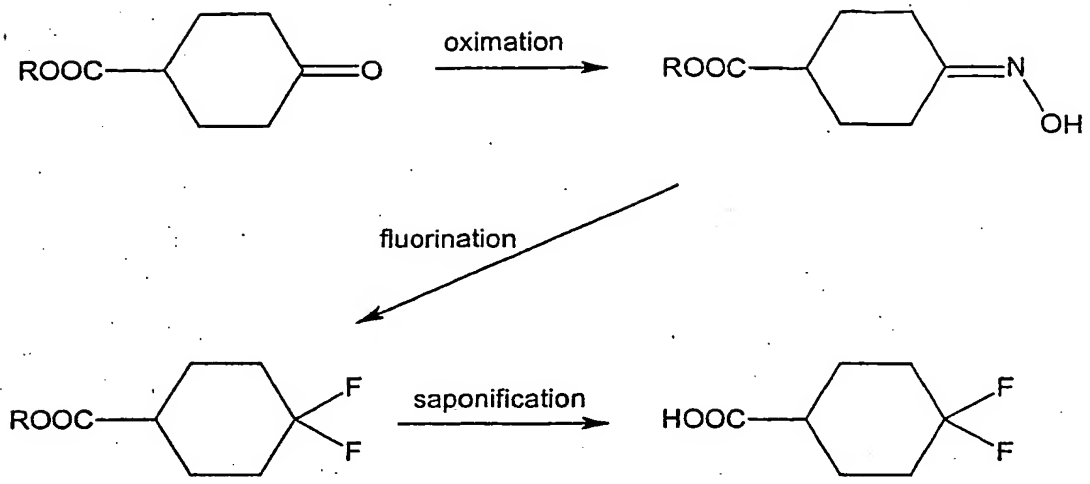
As the nitrite inorganic or organic nitrites, or a combination thereof can be used, however, for practical reasons, the use of sodium nitrite and/or potassium nitrite is preferred. If organic nitrites are used, pentylnitrite and butylnitrite are suitable candidates.

Preferably, the nitrite is added as a solid to the reaction mixture consisting of an oxime and onium poly(hydrogen fluoride). The reaction is highly exotermic and is carried out preferably at a temperature of about 0 °C. After conversion, the reaction mixture is further processed with water, as usual.

The starting materials and the reagents can be added in any order.

In order to provide the hydrogen fluoride with the necessary reactivity, the presence of an organic base is preferred. If nitrosyl tetrafluoroborate is used as a fluorination agent, this results in small yields, particularly for substituted oximes as shown in Comparative Example 1 below. Converting an oxime using only anhydrous HF and nitrite results in a very small yield as shown in a Comparative Example 2 below.

The reaction scheme for the production of the preferred compound 4,4-difluorocyclohexane-carboxylic acid can be shown as follows.



The following examples illustrate the above discussion.

Example 1

Preparation of 4,4-difluorocyclohexane-carboxylic acid ethyl ester (method A)

In a nitrogen deactivated 250 ml PFA-flask comprising a magnetic stirrer, a thermoindicator, an N_2-inlet, a dosing pipe with a single-use syringe, a bubble gauge and an exhaust tube, 100 g pyridine/HF with wt. 70% HF were added and cooled down to 0 °C. While stirring for 20 minutes, 6 g sodium nitrite were added in small portions. After continued stirring for another 10 minutes at 0 °C 8.6 g 4-cyclohexanoneoxime-carboxylic acid ethyl ester were added via a dosing pipe with a single-use syringe over a period of 55 minutes. Thereby, the temperature was kept constant in a range between -2 and 1.5 °C. Near completion of the dosing, gas was generated. The reaction mixture was then stirred for another 2 hours at 0 °C.

300 g ice were put in a 2l PE beaker, and the reaction mixture was poured in at constant stirring. The mixture was then extracted using 350 ml fluobenzene. Water was added to the combined organic phases, followed by neutralizing them with a saturated sodium hydrogen carbonate solution. After phase separation, the or-

ganic lower phase was washed with water, filtered and narrowed down. 5.77 g of the title compound were obtained (yield 64.7%), which was measured using gas chromatography.

Example 2

Preparation of 4,4-difluorocyclohexane-carboxylic acid ethyl ester (method B)

In a nitrogen deactivated 250 ml PFA-flask comprising a magnetic stirrer, a thermoindicator, an N_2-inlet, a dosing pipe with a single-use syringe, a bubble gauge and an exhaust tube, 100 g pyridine/HF with wt. 70% HF were added and cooled down to 0 °C. Then, 27.8 g 4-cyclohexanoneoxime-carboxylic acid ethyl ester were added via a dosing pipe with a single-use syringe over a period of 20 minutes after continued stirring for another 30 minutes at 0 °C. 12.4 g sodium nitrite were added in small portions. Thereby, the temperature was kept constant in a range between -2 and 1.5 °C. Near completion of the dosing gas was generated. The reaction mixture was then stirred for another 2 hours at 0 °C.

300 g ice were put in a 2l PE beaker, and the reaction mixture was poured in at constant stirring. The mixture was then extracted using 350 ml fluobenzene. Water was added to the combined organic phases, followed by neutralizing them with a saturated sodium hydrogen carbonate solution. After phase separation, the organic lower phase was washed with water, filtered and narrowed down. 18.2 g of the title compound were obtained (yield 63.0%), which was measured using gas chromatography.

Example 3

Preparation of 4-cyclohexanoneoxime-carboxylic acid ethyl ester

In a 500 ml three necked-flask comprising an stirrer, a cooler, a thermometer and a drip funnel, 200 ml water, 81.6 g sodium acetate and 52.2 g hydroxylamine hy-

drochloride were added and heated up to 60 °C. Then, 85.2 g 4-cyclohexanone-carboxylic acid ethyl ester were added to the mixture over a period of 1 hour. The emulsion was stirred for 1.5 hours and left to stand over night at room temperature. This was followed by adding 50 ml tert-butyl methyl ether, by shaking, by separating the lower phase and by a repeated extraction of 50 ml tert-butyl methyl ether. Then, the combined organic phases were washed several times with water, filtered, dried and narrowed down under reduced pressure. 86.8 g 4-cyclohexanoneoxime-carboxylic acid ethyl ester were obtained (yield 93.6%).

Comparative Example 1

Preparation of 4,4-difluorocyclohexane-carboxylic acid ethyl ester using $NOBF_4$

In a 200 ml PFA-flask with N_2-inlet, thermoindicator, dosing pipe with syringe, cooler, receiving flask, bubble gauge and exhaust tube, 100 g of pryidine/HF with 70 wt% HF were added and cooled down to 0 °C. Subsequently, 6.6 g nitrosyl tetrafluoroborate (white coarse crystals) were slowly added. 8.6 g of 4-cyclohexanone oxime carboxylic acid ethyl ester were drawn into a 10 ml syringe and added at -7 to -2 °C within 1 hour via the pipe. Then, the reaction mixture was heated up to room temperature and stirred for another 4 hours at room temperature. After about 1 hour the temperature rose to 27 °C, gas was bubbling up and N_2O could be observed in the bubble gauge. This was followed by cooling down with an ice bath. After the usual procedures, 3.4 g of the title compound (yield: 38.5%) could be isolated.

Comparative Example 2

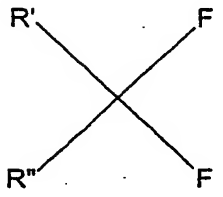
Preparation of 4,4-difluorocyclohexane-carboxylic acid ethyl ester using HF without an organic base

70 g of HF were put into a 250 ml PFA- round bottom flask which was cooled in an ice/sodium chloride-freezing mixture. At a temperature of about -10 °C 18.5 g of 4-cyclohexanone oxime carboxylic acid ethyl ester were added to the HF, followed by portionwise adding 7 g $NaNO_2$ to the solution within 2 hours. In the meantime, the flask was closed with a bubble gauge which was removed during the addition of the nitrite. Only a minor gas generation could be observed. The reaction temperature was limited to a range between -5 °C and 2 °C. After dosing the nitrite, the reaction mixture was poured on ice, and after phase separation a sample was taken from the organic phase.

The GC-analysis showed 84 area% starting material, 7.6 area% of 4,4- difluoro-cyclohexane-carboxylic acid ester and 5.6 area% of a monofluoro-compound. The assignment was performed using GC/MS.

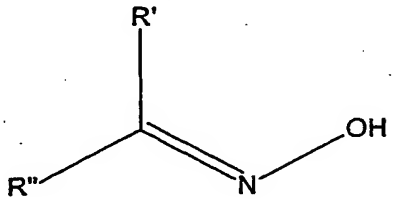
Claims

1. Process for the preparation of a geminal difluoroalkane of the general formula (I),



(I)

wherein, independently from each other, R' and R" represent substituted alkyl-, aryl- or aralkyl or may be combined by the formation of a cyclic system, characterized in that an oxime of the general formula (II)



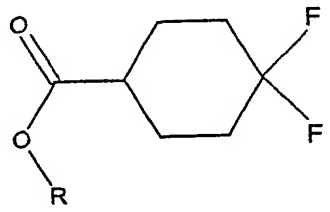
(II)

whereas R' and R" are defined as aforesaid, is converted using a nitrite and a complex consisting of hydrogen fluoride and an organic base.

2. Process according to claim 1, characterized in that R' and R" represent C_1 - C_8-alkyl or aryl or, in combination with the carbon atom they are bound to, C_3 - C_8-alkyl.

3. Process according to claim 2, characterized in that R' and R" form a cyclohexane ring in combination with the carbon atom they are bound to.

4. Process according to claim 3, characterized in that the difluoroalkane of the general formula (I) is a difluorocyclohexane-carboxylic acid ester of the general formula (I'),



(I')

wherein R represents a hydrogen atom or C_1 - C_8-alkyl.

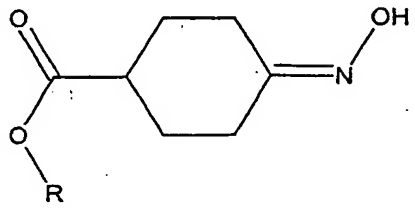
5. Process according to claim 4, characterized in that the difluoroalkane of the general formula (I') is 4,4-difluorocyclohexane-carboxylic acid ethyl ester.

6. Process according to claim 4, characterized in that the difluoroalkane is 4,4-difluorocyclohexane-carboxylic acid.

7. Difluorocyclohexane-carboxylic acid ester of the general formula (I') according to claim 4, wherein R represents a hydrogen atom or a C_1 - C_8-alkyl residue.

8. Compound according to claim 7, namely 4,4-difluorocyclohexane-carboxylic acid.

9. Compound according to the general formula (II')



(II')

wherein R represents a hydrogen atom or a C_1 - C_8-alkyl residue.

10. Use of 4,4-difluorocyclohexane-carboxylic acid as an intermediate in the manufacture of pharmaceutical products.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/005756

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C67/307 C07C69/75 C07C51/363 C07C61/15 C07C251/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data, PAJ, INSPEC, COMPENDEX

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search	Date of mailing of the international search report
21 October 2004	18/11/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seelmann, M

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/005756

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/005756

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Information on patent family members

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